Brain-injured Survivors of Monochorionic Twin Pregnancies Complicated by Single Intrauterine Death: MR Findings in a Multicenter Study:

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Manuscript title: MR findings in brain injured survivors of monochorionic twin pregnancies complicated by single intrauterine death: a multicenter study.

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Implications for patient care: This study provides new information about the characteristics of fetal brain abnormalities in surviving co-twins of monochorionic twin pregnancies complicated by single intrauterine death. This information is valuable for accurate counselling and informed management planning.

Summary statement: Ischemic lesions predominate in brain injured survivors after single intrauterine death in monochorionic twin pregnancy and are more likely to be focal (embolic) in pregnancies complicated by twin-twin transfusion syndrome or after obstetric intervention.

Abstract

Objective: To describe and classify the range of brain injuries present on prenatal, in-utero magnetic resonance (iuMR) studies in co-twin survivors of monochorionic (MC) mutifetal pregnancies complicated by single intrauterine death (sIUD).

Methods: This is a retrospective, observational study from six tertiary fetal medicine centres performing tertiary level prenatal iuMR studies. We reviewed cases in which prenatal iuMR imaging had shown a brain injury in a surviving co-twin of a multi-fetal pregnancy with a MC component, complicated by sIUD.

Results: Forty-two surviving MC twins are described. The primary distinction of brain abnormalities was into non-focal and focal lesions. The non-focal lesions included: periventricular leukomalacia (group 1 – two cases), generalised encephalomalacia (group 2 – nine cases), posterior encephalomalacia (group 3 – seven cases) and bilateral para-sagittal and peri-sylvian lesions (group 4 – three cases). The focal lesions included: non-hemorrhagic lesions (group 5 – 14 cases) and hemorrhagic lesions (group 6 – seven cases). Focal brain lesions were more likely to be found in the surviving MC pregnancies complicated by TTTS (odds ratio = 2.4; 95%CI: 1.3-18.5; p=0.01) and in fetuses that had had an obstetric intervention (odds ratio = 2.8, 95%CI: 1.8-23.6; p=0.006).

Conclusion: Brain injury of the surviving co-twin after sIUD in MC pregnancies is usually of ischemic origin and spares the brainstem/cerebellum. Focal brain lesions are more frequent in pregnancies complicated by TTTS or in those where an intervention has been performed. We hypothesize that those focal lesions are most likely to be the result of thromboembolic complications.

Keywords: magnetic resonance imaging; prenatal diagnosis; monochorionic twin pregnancy; brain; single intrauterine death.

Introduction

Multi-fetal pregnancies are high-risk when compared with singleton pregnancies in terms of increased perinatal mortality rates [1,2], and have a high risk of single-fetus intrauterine death (sIUD), complicating up to 6% of twin pregnancies after the second trimester [3]. The 'impact' of this event is very dependent upon chorionicity [4,5] with a recent meta-analysis of the literature demonstrating increased mortality (15% vs 3%) and neurodevelopmental morbidity (26% vs 2%) in the surviving co-twins of monochorionic (MC) pregnancies compared with those of dichorionic pregnancies [6]. In this critical appraisal of the literature, abnormal postnatal cranial imaging in MC twins was noted in 36% of pregnancies [6]. sIUD in MC pregnancies may be spontaneous or follow an obstetric intervention, such as selective feticide or fetoscopic laser therapy for twin-twin transfusion syndrome (TTTS) [4]. Prenatal identification and characterization of fetal brain abnormalities in a surviving co-twin is critical for accurate counselling and informed management planning. There is increasing evidence that prenatal, in-utero (iu) MR imaging provides the best opportunity for accurate diagnosis of fetal brain abnormalities [7] but there are relatively few studies of brain abnormalities in co-twin survivors in MC pregnancies. The early literature suggests that prenatal iuMR imaging may detect the brain abnormalities [8-10] and a range of pathologic types have been described [11-13]. The largest of these cohort studies included 13 fetuses with brain abnormalities. However, only four (31%) of those had prenatal iuMR imaging [13]. Small sample sizes have prevented authors from providing a useful classification system of the brain abnormalities present in such cases and this makes drawing inferences about the etiological causes difficult or impossible.

The primary objective of this study was to analyze prenatal iuMR studies of cases of sIUD from MC pregnancies with fetal brain abnormalities in the surviving co-twin in order to

produce a classification system that may be used in future multi-centre prospective studies. The secondary objective was to consider if there are patterns of brain injury that would help in developing hypotheses about etiological mechanisms of injury.

Materials and Methods

Caseload and ethical approval

This is a retrospective, observational study from six tertiary fetal medicine centres or departments performing tertiary level prenatal MR studies in Italy and England, namely;*BLINDED*.

The cases from *BLINDED* were recruited as clinical cases with ethical approval for retrospective review of clinical notes and MR images by the local Ethics Committees, without the need for specific consent from patients. For the cases from *BLINDED* no ethical committee approval was necessary according to national regulations because this was a retrospective analysis of routinely collected anonymised clinical data. Approval for use of the cases from *BLINDED* was provided by *BLINDED* Ethics Committee. The cases from *BLINDED* were either recruited as research cases after written informed consent with approval from *BLINDED* Ethics Committee or as clinical cases with the approval of the *BLINDED*. Those cases (four) were included in an earlier publication whose aim was to quantify the risk of brain abnormalities after single-twin demise in monochorionic pregnancies [12]. In contrast our aim was to classify the range of brain injuries found on in-utero MRI in a large cohort of brain-injured survivors of monochorionic multifetal pregnancies complicated by **sIUD**. This differs to the previously published article and required a multicenter approach and inclusion of the four previously published cases. All cases were anonymised.

Each institution's radiology database was searched for **consecutive** prenatal MR studies performed in a 14-year period between January 2002 and December 2015 looking for cases that fulfilled the following criteria:

1. Multi-fetal pregnancy with a MC component (twin or triplet) confirmed by established criteria [14].
2. Ultrasound confirmation of *in utero* death of one of the MC fetuses.

This study includes all of the cases where brain parenchymal abnormalities of the surviving fetuses were confirmed by consensus expert review of the prenatal MR studies. (NB fetuses with ventriculomegaly only were not included).

Clinical information was retrieved from the local databases of the participating centres and the following details were extracted;

1. Twin or triplet MC pregnancy.
2. The estimate at when sIUD of the MC twin occurred – taken as the mid-point of the gestational age at which both (all) fetuses were alive and the first documentation of sIUD.
3. Gestational age at which the prenatal MR study was performed, hence estimating the fetal demise to MR period.
4. Presence or absence of TTTS.
5. Surgical intervention (fetoscopic laser surgery or selective feticide) performed or not (classified subsequently as 'spontaneous' sIUD).
6. Time interval between surgical intervention and sIUD.

Gestational age was determined using the best estimate of delivery date obtained from biometric data from the second trimester US.

MR imaging and analysis

All prenatal MR exams were performed at 1.5 Tesla using either a phased-array abdominal or cardiac coil, although the MR protocols were different at each centre because of the retrospective nature of the study. The following sequences were absolute requirements for inclusion and review in this study; T2-weighted ultra-fast images of the fetal brain in three orthogonal planes and T1-weighted gradient-echo or fast spin-echo images in at least one plane. An expert panel consisting of two pediatric neuroradiologists (G.C. and A.R.) reviewed a random subgroup (n=20) of the total caseload by consensus in order to create groups of brain abnormality types. They also provided anonymised, single images of representative examples from each of the defined six groups in order to assist the analysis by the second expert panel described below.

The formal analysis involved image review of all of the confirmed prenatal MR cases by a second panel of three neuroradiologists (P.D.G., N.S., M.I.) by consensus. They were blinded to all of the clinical information except the gestational age at which the prenatal MR was performed and if the pregnancy was twin or triplet. The reviewers first ascribed each case to one of the six categories of brain abnormality set by the first panel and then provided a more detailed report on each case based on the perceived nature of the lesion and its location(s).

Statistical analysis

Nominal data is expressed as absolute or relative frequencies and quantitative data is expressed as median and interquartile range (IQR). The data was analysed further by considering the pathology as either non-focal (groups 1-4) or focal (groups 5-6) pathology as described in the results section and explained in the discussion. The frequency of those binary groups of lesion type were calculated by forming 2x2 tables for the TTTS and non-TTTS cases and a χ^2 test was used to look for differences. Continuous data were compared between

those binary groups using a Mann-Whitney test. A similar procedure was undertaken for 'obstetric intervention' or 'spontaneous loss' pregnancies. Differences were considered statistically significant if $p<0.05$. The statistical analysis was performed with SPSS 20 statistical software (IBM Corporation, Armonk, NY).

Results

Forty-two fetuses met the entrance criteria (see supplemental Figure 1 for the flow-chart of fetus enrolment criteria): 38 from MC twin pregnancies (34 monochorionic/diamniotic and four monochorionic/monoamniotic) and four from triplet pregnancies (all dichorionic/triamniotic) with demise of a fetus in the MC environment. TTTS complicated 22/42 (52%) of the pregnancies and in 11 of those cases the recipient twin was the survivor, in five cases the donor twin was the survivor and in six cases details about the surviving fetus were not recorded (in terms of donor or recipient). Fetoscopic laser therapy was performed in 14 of the cases complicated by TTTS and selective feticide was performed in four cases overall (in case 3 and 26 for TTTS, in case 9 and 42 for a discordant anomaly) as detailed in Figure 1 and Tables 1 and 2. The median gestational age at sIUD and MR imaging was 21 weeks (IQR 18-24 weeks) and 24 weeks (IQR 21-26 weeks), respectively. The median sIUD to MR interval was 3 (IQR 1-4) weeks. The primary distinction made by the first assessment panel was between non-focal or focal lesions, the rationale for this approach is explained in the discussion. The lesions were then further divided into four types of non-focal lesions, and two types of focal lesions, based on location, extent and nature as detailed in Figure 2 and illustrated in Figure 3.

The second panel (based on their review of the images blinded to the clinical information about the pregnancies) judged that 21/42 (50%) fetuses had non-focal brain lesions and 21/42

(50%) fetuses had focal brain lesions with the number of fetuses attributed to each group shown in Figure 2 and the clinical information relating to all of the pregnancies presented in Table 1 and 2. There were no statistically significant differences between the non-focal and focal group f**or the variables represented in Table 3.**

The commonest groups of brain abnormalities were non-haemorrhagic focal lesions (group 5) 14/42 (33%) and generalised encephalomalacia (group 2) 9/42 (21%). Focal brain lesions (groups 5 and 6) were more likely to be found in the surviving co-twins from pregnancies complicated by TTTS when compared with those with no history of TTTS (odds ratio 2.4, 95% CI: 1.3-18.5) and the difference was statistically significant (**Table 4**). Focal brain lesions were also more likely to be seen in fetuses that had had some form of obstetric intervention when compared to the non-intervention group (odds ratio 2.8, 95% CI: 1.8-23.6) (**Table 5**).

The more detailed anatomical analysis of lesions showed that 35/42 (83%) brain lesions were considered to be ischaemic in nature and seven were haemorrhagic (six purely haemorrhagic and one mixed). Only 1/42 fetuses (2%) had an infra-tentorial brain abnormality, which was a focal cerebellar haemorrhage and involvement of the basal ganglia was also infrequent occurring in 5/42 fetuses (12%). In group 5 (non-haemorrhagic focal lesions) 8/14 cases had abnormalities of the cortical plate or cerebral cortex thought to represent a region of focal polymicrogyria related to the focal ischaemic lesion (Figure 3.5 and **Supplemental Figure 2**).

Discussion

This study demonstrates the wide spectrum of lesions that may result from injury to the brain of co-twin survivors of MC pregnancies complicated by demise of one twin. It should be appreciated that the purpose of this study was not to estimate the prevalence of brain injuries

in co-twin survivors of MC pregnancies and our data cannot be used for that purpose as a brain abnormality was an entrance requirement for the study. In a systematic review by Ong et al, including 17 studies with a total of 267 pregnancies, the prevalence of neurological abnormalities in this group has been estimated at 18% (95% CI: 11-26) demonstrating that neurological abnormalities are a substantial problem in this group [15].

We have shown that the cerebral hemispheres are the main site of brain injury in co-twin survivors, with brainstem/cerebellar involvement in only 1/42 fetuses in our series. These findings are consistent with the limited number of reports of previous cohort studies, for example, Van Klink et al. did not report any brainstem/cerebellar lesions [13] and Donoghue et al. reported only one cerebellar lesion [11]. The pathophysiological explanation of the relative sparing of the brainstem/cerebellum is far from clear, but it is interesting to note that both our case and the one in the earlier literature describe focal haemorrhagic lesions in the cerebellum. Sparing of the brainstem/cerebellum may be related to preferential preservation of blood supply from the posterior (vertebro-basilar) circulation during episodes of generalized reduced perfusion pressure and this is a well-recognised feature of ischemic-hypoxic injury in neonates [16]. It should be noted, however, that ‘posterior encephalomalacia’ (group 3 lesions) were quite common in our series (7/41 fetuses) and the brain regions involved in group 3 lesions are often supplied by the posterior circulation.

Hemorrhagic lesions in this study were defined as areas of brain injury with abnormal low signal on T2-weighted and/or high signal on T1-weighted images due to the presence of either deoxyhemoglobin, methemoglobin or hemosiderin. These lesions were focal in our cases and we propose that most occurred by hemorrhagic change in brain tissue previously injured by ischemia/infarction. We do not know the contribution of any possible coagulopathy in the surviving fetus to the development of hemorrhagic brain lesions. The

relatively low proportion of hemorrhagic lesions in our study (17% v 83% non-hemorrhagic) is in agreement with previous studies [11 - 13].

There are a number of possible mechanisms that could lead to brain injury in survivors after sIUD [4] and the two leading theories are thromboembolic and hypoxic/ischemic. **A speculative theory** is that thrombus may form in the vascular compartment of the demised fetus (or the associated placental tissue) and create emboli that pass to the surviving twin because of persisting flow in placental anastomotic vessels. Those emboli may lodge in the cerebral blood vessels of the surviving fetus and cause focal ischaemic lesions best classified as arterial infarctions [17,18]. According to the published literature, a more likely cause of brain injury results from a generalised hypoxic/ischemic event [19-21]. The mechanism for this is uncertain but may be due to the low-pressure vascular compartment of the demised fetus producing acute exsanguination of the survivor leading to low perfusion pressure, anaemia and hence brain injury. Neuroimaging experience from neonates, children and adults predicts that these mechanisms would produce different patterns of brain injury. Specifically, thrombo-embolic phenomena will tend to produce focal (or multi-focal) lesions (either non-hemorrhagic or hemorrhagic) whilst brain injury resulting from generalised reduced perfusion pressure will tend to produce bilateral (often symmetrical) injury in vascular watershed regions of the brain. This was the reason for using ‘focal’ and ‘non-focal’ lesions as the primary discriminant in our anatomical classification of fetal brain injuries.

Non-focal (groups 1-4) and focal brain lesions (groups 5 and 6) were found in co-twin survivors in equal proportions (21/42 fetuses had focal brain lesions and 21/42 fetuses had non-focal lesions). We have shown that there was a statistically significant greater chance of focal brain abnormalities occurring in co-twin survivors from MC pregnancies complicated by TTTS when compared with pregnancies without TTTS ($p=0.01$). Similarly, we have shown a statistically significant greater chance of focal brain abnormalities in the co-twin

survivors from MC pregnancies in which an obstetric intervention has been performed when compared with 'spontaneous' twin demise ($p<0.01$). We believe that this observation supports the **speculative** theory that thromboembolic phenomena are more likely to occur in TTTS cases and after interventional procedures for the reasons explained above. It should be appreciated, however, that the TTTS and intervention groups are not strictly independent as MC pregnancies complicated by TTTS are far more likely to have an obstetric intervention than one without TTTS. More data are required to look at the frequency of focal brain lesions in cases of TTTS without an obstetric intervention, and intervention for selective feticide, compared with laser intervention to delineate if the focal lesions are part of the pathophysiology of TTTS, or a consequence of laser therapy. Unfortunately, due to the rapid progression of TTTS and the need for timely laser therapy, a study comparing pre-laser therapy MR and post-laser therapy MR would be logistically difficult.

If we are correct and non-focal brain injury (groups 1-4) arises from a generalised reduction in perfusion pressure and anemia, it is interesting to speculate why we see different patterns of generalised injury, i.e. periventricular leukomalacia (group 1), generalised encephalomalacia (group 2), posterior encephalomalacia (group 3) and bilateral parasagittal/peri-sylvian lesions (group 4). We do not have a sufficient number of cases to perform reliable inferential statistics but a possible influential factor may be the gestational age at which sIUD of the fetus occurred, and presumably the brain damaging event in the surviving co-twin. It is possible, for example, that posterior encephalomalacia (group 3) may be the typical injury in less mature fetuses because of higher energy consumption and blood flow in those areas early in brain development [22]. In contrast, the patterns of injury described in groups 1,2 and 4 may reflect the predominant pattern of hypoperfusion injury in more mature fetuses resembling the sequelae of prolonged partial hypoxia-ischemia in fetuses/neonates closer to term [23]. Again, this theory needs to be tested in further studies.

The association between non-hemorrhagic focal injuries (group 5) and abnormalities of cortical formation in cases of surviving co-twins of MC pregnancies has been described in previous publications [24, 25] and we have noted interesting interval changes in two of our cases in this report. Case 12 was the surviving fetus (donor) of a TTTS pregnancy with sIUD of the recipient co-twin after laser-therapy at 18 weeks gestation. The prenatal MR imaging at 21 weeks (2 weeks after sIUD) showed a non-haemorrhagic focal brain lesion (group 5) described as focal thinning of cortical mantle in the right para-central region (**Supplemental Figure 2a**). Not many of our cases had more than one prenatal MR study but in this case an interval study was performed at 25 weeks (6 weeks after sIUD) (**Supplemental Figure 2b**). The area previously described as abnormal thinning of the cortical mantle showed more prominent focal atrophy but the invaginated surface had a prominent, and probably abnormal, cortical plate and postnatal MR imaging confirmed an area of focal polymicrogyria (**Supplemental Figures 2c and 2d**). This further highlights the importance of acquired pathology in the etiology of some brain lesions typically thought of as 'developmental' in origin and this type of pathology is often referred to as "reparative polymicrogyria" [24]. Case 42 was the surviving co-twin from an MC pregnancy without TTTS in which selective feticide was performed at 20 weeks. Bilateral, symmetrical posterior encephalomalacia (group 3) was identified on prenatal MR at 21 weeks (**Supplemental Figure 3a**). A repeat prenatal MR study was performed at 27 weeks and showed extensive loss of brain volume from the posterior half of the left cerebral hemisphere with communication between the lateral ventricle and the external CSF spaces (**Supplemental Figure 3b**). Cortical plate lines the cleft allowing a diagnosis of "open lip" schizencephaly to be made. This case supports the notion that schizencephaly, as well as polymicrogyria, can result from brain pathology acquired in the second trimester.

There are several limitations to our study, primarily resulting from the retrospective nature of the case collection. **The exclusion of fetuses with isolated borderline ventriculomegaly could be considered a limitation of the study. However, it should be noted that in all excluded cases the ventriculomegaly was mild (atrial diameter <12 mm) with no evidence of parenchymal lesions.**

We were not able to standardise the MR scan protocols across the collaborating centres and the interval time between sIUD and MR imaging was also not standardised. The timing of the prenatal MR scan in relation to sIUD is likely to have an important effect on the ability to detect and accurately classify brain lesions. Most of the pre-natal MR scans of co-twin survivors were performed a small number of weeks after the demise of the co-twin, with only 4/42 MR studies performed within one week. This should make our lesion characterization more robust, as early assessment may overlook or mis-classify evolving pathology. The use of diffusion weighted imaging (DWI), however, should allow the detection of ischemic lesions within one day of co-twin demise [26,27,28] and be useful for approximately seven days after demise when pseudo-normalisation is expected. In spite of that, we believe that a complete and reliable assessment of brain damage is best performed with higher resolution ssFSE T2-weighted sequences after 7 days from the demise. We have already explained that at the start of the study some of the authors had the *a priori* belief that the anatomical pattern of brain injuries would provide insight into the etiological cause and this had the potential to bias our results. We mitigated against this by designing the study so that the second radiological panel (who were providing the information used in the results) were blinded to the clinical background of the case i.e. they were not aware if they were reporting on a TTTS case or a pregnancy with an obstetric intervention. Although this cohort is by far the largest described in the literature, we have not been able to perform multivariate analyses to confirm the independent value of the significant variables (TTTS vs non-TTTS and intervention vs

no-intervention) in predicting the type of brain lesion in MC co-twin survivors. A further limitation is the lack of data about post-natal clinical outcomes and imaging in most cases, but this is a topic for future work.

In conclusion, sIUD in MC pregnancies can lead to a range of brain injuries in the surviving co-twin and these are usually ischemic and spare the brainstem/cerebellum. We have developed a six-group classification system for brain injury in surviving twins that may assist in designing future prospective MR studies, as well as helping neuroradiologists in clinical practice. Our data show that focal brain lesions are more frequent in pregnancies complicated by TTTS or in which an obstetric intervention has been performed and we suggest that this implicates thromboembolism as the likely cause of such injury.

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Figures captions:

Figure 1: Description of 42 surviving fetuses with MR detected brain abnormalities in monochorionic pregnancies complicated by the demise of one fetus. The number of * indicates the number of triplet pregnancies in each group. *Abbreviations*: TTTS = twin-twin transfusion syndrome, sIUD = single *in utero* death.

Figure 2: Classification system with the six groups of brain abnormalities and the number of fetuses in each group.

Figure 3: Examples of brain abnormalities from the six groups. 3.1 Periventricular leukomalacia (Group 1); 3.2 Generalised encephalomalacia (Group 2); 3.3 Posterior encephalomalacia (Group 3); 3.4 Parasagittal and perisylvian injury (Group 4); 3.5 Focal, non-haemorrhagic lesions (Group 5); 3.6 Focal, haemorrhagic lesions (Group 6).